

De Novo Hepatocellular Carcinoma in a Patient with Chronic Hepatitis C 5 Years After Sustained Virologic Response to Interferon/Ribavirin Therapy

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Screening for hepatocellular carcinoma (HCC) is an accepted component of the long-term management of patients with chronic hepatitis C and cirrhosis. Current interferon-based regimens clear hepatitis C in approximately 50% of treated patients. Clearance is associated with improvement in liver histology, stabilization of liver disease, and, possibly, reduction in risk of HCC. One result of the improvement in therapy is an increasing number of patients with advanced fibrosis or cirrhosis who will have achieved sustained virologic remission. An important clinical question is whether to screen for the development of HCC, particularly in noncirrhotic patients, after a sustained response to antiviral therapy. Herein we report a case of a hepatitis C virus (HCV)-infected patient, Metavir fibrosis stage 3, who has sustained virologic response to antiviral therapy, but developed HCC 5 years after the completion of therapy.

CASE PRESENTATION

A 50-year-old asymptomatic Hispanic man had abnormal liver tests during a routine physical in 1989. Liver biopsy demonstrated mild chronic active hepatitis with no cause of liver disease defined. His diagnosis was non-A, non-B hepatitis, and liver tests were monitored. Social history was only remarkable for remote, brief experimentation with intravenous drugs at age 17.

In 1996, he was reevaluated; hepatitis C antibody was positive and he had a firm liver edge and palpable spleen. Laboratory tests demonstrated AST 121 IU/L, ALT 180 IU/L, platelet count 115,000/ μ L, albumin 4.3 g/dL, and prothrombin time 13.9 sec. HCV genotype was 1b with HCV RNA quantitation of 1,831,250 copies/mL. Repeat liver biopsy revealed chronic active hepatitis, grade 3, stage 3. The patient was treated with interferon alfacon-1 monotherapy (Infergen, 9 μ g tiw) but failed to respond. He was retreated with the combination of interferon alfa-2b (Intron A) plus ribavirin (Rebetol), cleared HCV RNA, and had sustained virologic response. His last dose of treatment was in October, 1999, and he has had normal ALT and undetectable HCV RNA on annual testing since completion of therapy.

He subsequently underwent annual screening for HCC using alpha-fetoprotein and ultrasonography. In 2004, nearly 5 years after finishing therapy with a sustained response, a 2.0-cm hypoechoic but solid-appearing mass was identified on ultrasound. The patient had no clinical or biochemical evidence of decompensation. Follow-up computed tomography and magnetic resonance imaging (MRI) of the abdomen confirmed the presence of a mass in the medial segment of the left lobe with ring enhancement concerning for a malignant process (Figure 1). Alpha-fetoprotein levels were normal. The patient underwent laparoscopic biopsy of the lesion which confirmed a diagnosis of HCC. Radiofrequency ablation of the mass was performed and the patient was listed for hepatic transplantation. The patient successfully underwent transplantation and pathologic examination of the explanted liver confirmed the presence of HCC in the setting of bridging fibrosis (Metavir stage 3).

DISCUSSION

HCC affects approximately half a million persons each year worldwide. In the United States, the age-adjusted incidence of HCC has doubled from 1.4 per 100,000 during 1976–1980 to 3.0 per 100,000 during 1996–1998. These figures underestimate the true incidence as they

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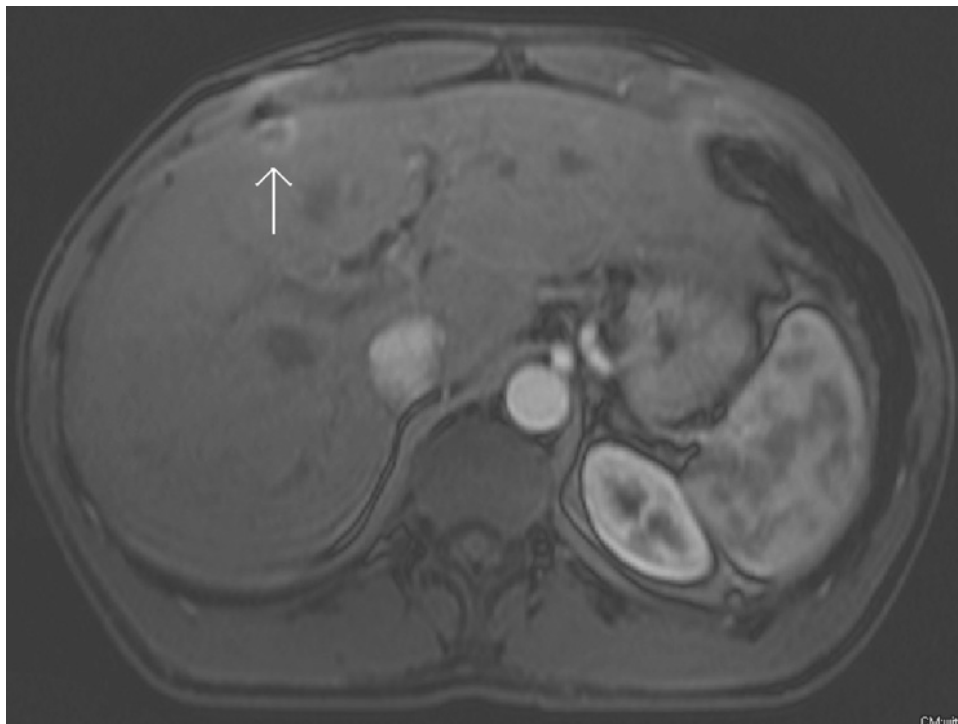


Fig 1. T₂ axial MRI image of 1.2- × 1.3-cm mass in medial segment of the left liver lobe.

represent only HCCs which have been confirmed by histopathologic examination. The overall age-adjusted mortality rate for HCC has increased at a similar rate (1).

HCV infection plays an important role in these trends. Along with alcohol consumption, hepatitis B virus (HBV) infection, and cirrhosis, HCV infection is recognized as a major risk factor for HCC (2). Given the current prevalence of HCV infection among U.S. adults aged 30–50 years, the incidence and mortality rates of HCC are predicted to double over the next 10–20 years.

The precise mechanism by which HCV infection causes HCC is not known. The development of cirrhosis is usually the cause of HCC in HCV infection, but there is evidence to suggest that HCV could also have direct oncogenic effects (3). HCV RNA is detectable in the serum, liver, and tumor tissues of patients with HCC. Unlike HBV, it does not integrate into the host genome (4), so the virus would have to exert its oncogenic effects from an extra-chromosomal position. A recent study found consistent differences in gene expression patterns in HCV-HCC compared with early HCV cirrhosis, late HCV cirrhosis, and normal controls (5). There were also different patterns between early and advanced HCC tumor stages. Further studies are needed to elucidate the causes of HCV related carcinogenesis.

It has been suggested that long-term suppression of viral replication could reduce hepatocyte turnover and decrease the risk of dysplasia and cancer. In 1995, a small prospective, randomized, controlled trial (RCT) showed a significant reduction of HCC in HCV-related cirrhosis treated with interferon, 4% versus 38% (6). Since that time, many nonrandomized and several RCTs have been published. Meta-analysis of these trials also suggested a decreased risk of HCC in patients with HCV-related cirrhosis treated with interferon (7). The benefit is clearly higher when a sustained biochemical response to IFN is obtained with a number needed to treat of 5. There is, however, significant heterogeneity among these studies and an inherent difficulty in determining the presence or absence of cirrhosis in these treated patients.

We are unaware of any reports in the United States of the development of HCC after successful antiviral therapy. The case presented is notable for several other reasons. The patient had no other risk factors for HCC such as alcohol use, coinfection with HBV, or established cirrhosis. During treatment and subsequent follow-up, the patient had no evidence of recurrent HCV infection or clinical decompensation. Furthermore, the development of HCC in this case occurred long after completion of antiviral therapy. It is highly unusual to develop HCC this late after successful antiviral therapy.

There are several similar cases reported in the Japanese population, but no cases of HCC development after successful antiviral therapy have been reported outside of Japan. Review of Japanese cases does reveal some significant differences from the case presented. The majority of Japanese cases had developed HCC within 1 year of completing treatment (8). Also, interferon monotherapy was the sole treatment in these reported cases (9–11).

More importantly, there is evidence to suggest that HCC is a different disease in the Japanese population, and it may be inappropriate to extrapolate the Japanese experience to other places such as the United States. Asian men have the highest age-adjusted incidence rates of HCC (1). The development of HCC in patients without cirrhosis is routinely reported in Japan, even with mild degrees of fibrosis (12). Finally, most patients with cirrhosis in Japan die from HCC-related complications rather than other cirrhosis-related complications (13), suggesting that unknown genetic or environmental factors might explain the high incidence of HCC in HCV-infected Japanese patients.

The case presented addresses a major question in management of patients after successful antiviral therapy, “Should HCV-infected patients with a sustained response to antiviral therapy undergo screening for HCC?” Our case report indicates that these patients, particularly those with stage 3 disease or greater on biopsy or other clinical evidence of early cirrhosis, are at risk for cancer and that screening can identify treatable HCCs. For these reasons, we suggest serial ultrasonography and serum alpha-fetoprotein levels in HCV-infected patients with stage 3 disease or greater on biopsy who have a sustained response to antiviral therapy.

REFERENCES

1. El-Serag HB: Hepatocellular carcinoma and hepatitis C in the United States. *Hepatology* 36:S74–S83, 2002
2. Di Bisceglie AM: Hepatitis C and hepatocellular carcinoma. *Hepatology* 26:34S–38S, 1997
3. Ray RB, Meyer K, Ray R: Suppression of apoptotic cell death by hepatitis C virus core protein. *Virology* 226:176–182, 1996
4. Sherlock S: Viruses and hepatocellular carcinoma. *Gut* 35:828–832, 1994
5. Mas VR, Maluf DG, Stravitz R, *et al.*: Hepatocellular carcinoma in HCV-infected patients awaiting liver transplantation: Genes involved in tumor progression. *Liver Transpl* 10:607–620, 2004
6. Nishiguchi S, Kuroki T, Nakatani S, *et al.*: Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 346:1051–1055, 1995
7. Camma C, Giunta M, Andreone P, Craxi A: Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: An evidence-based approach. *J Hepatol* 34:593–602, 2001
8. Sugiura N, Sakai Y, Ebara M, *et al.*: Detection of hepatocellular carcinoma after interferon therapy for chronic hepatitis C: Clinical study of 26 cases. *J Gastroenterol Hepatol* 11:535–539, 1996
9. Sugo H, Kitayama N, Iwata T: Development of hepatocellular carcinoma in a patient with chronic hepatitis C after a complete response to interferon therapy. *Acta Hepat Jpn* 41:195–198, 2000
10. Yamada M, Ichikawa M, Matsubara A, Ishiguro Y, Yamada M, Yokoi S: Development of small hepatocellular carcinoma 80 months after clearance of hepatitis C with interferon therapy. *Eur J Gastroenterol Hepatol* 12:1029–1032, 2000
11. Makiyama A, Itoh Y, Kasahara A, *et al.*: Characteristics of patients with chronic hepatitis C who develop hepatocellular carcinoma after a sustained response to interferon therapy. *Cancer* 101:1616–1622, 2004
12. Yoshida H, Shiratori Y, Moriyama M, *et al.*: Interferon therapy reduces the risk for hepatocellular carcinoma: National surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. *Ann Intern Med* 131:174–181, 1999
13. Kato Y, Hamasaki K, Aritomi T, Nakao K, Nakata K, Eguchi K: Most of the patients with cirrhosis in Japan die from hepatocellular carcinoma. *Oncol Rep* 6:1273–1276, 1999